Original Article

Headache Associated with Hemodialysis in Patients with End-Stage Renal Disease in India: A Common Yet Overlooked Comorbidity

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Abstract

Background: Headache is a frequently encountered symptom among patients undergoing hemodialysis. **Aim:** The aim of this study was to elucidate the prevalence of hemodialysis associated headache (HDH), its possible etiology, its effect on the patients and steps taken in the management of the condition in Indian patients with end-stage renal disease (ESRD). **Methods and Materials:** A cross-sectional study was carried out amongst 128 consenting patients with ESRD on regular hemodialysis at a tertiary care medical teaching hospital over a period of 3 months to assess for prevalence of HDH and factors related to it. The pre hemodialysis serum electrolytes level, pre and post hemodialysis systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Visual analogue scale (VAS) and patient health questionnaire-9 (PHQ9) was administered to the patients. *t* Test and Chi-square test were applied to find the association between HDH and various postulated factors and a regression analysis was performed. **Results:** Among 128 patients, 48 (37.5%) (men 18 [37.5%], women 30 [62.5%]) were found to have HDH. The mean headache severity scores on (VAS) was 4.5 ± 1.74. Patients having HDH had their mean PHQ9 scores 7.56 ± 4.51. Most patients had headaches in the first hour of dialysis and were located in the frontal and temporal part of the head. No statistically significant difference was found in the electrolyte levels between patients having HDH and without HDH**.** The headache was moderate in most but needed a paracetamol tablet to relieve the headache. **Conclusion:** Nearly one-third of patients undergoing dialysis have HDH, and it is associated with mild to moderate depression. The factors leading to HDH and its management need to be evaluated further to improve the quality of life of patients with ESRD on dialysis.

Keywords: Chronic kidney disease, depression, hemodialysis, hemodialysis headache

Introduction

Patients with end-stage renal disease (ESRD) on maintenance hemodialysis (MHD) are often found to suffer from headaches during and following the dialysis sessions. Hemodialysis headache (HDH) was first described by Bana *et al.*[1] in 1972 and in 1988 International Headache Society (IHS) gave a detailed description of the same. HDH generally starts during the sessions and resolves after the session within 72 h.[2] It was suggested that changes in the electrolytes during the hemodialysis session could be a reason for headache to develop which may be attributed to dialysis disequilibrium syndrome.[1] In the International Classification of Headache Disorders-3 (ICHD3), it is classified under the subheading of headache disorders attributed to disorders of homeostasis.[2] Different etiology were proposed in further studies that included changes in electrolytes during dialysis, hypertension, bone mineral disorder, mental health of the patient among many others. ICHD3 beta classification has well defined criteria for HDH.[3] There is a lack of data with regards to prevalence of HDH amongst Indian patients with ESRD undergoing MHD. However, headache is found to be a common symptom amongst these patients in clinical practice. It is necessary to identify the high-risk individuals, accurately diagnose it, take steps for its prevention and management, and improve the wellbeing of the patients. We initiated this study to elucidate the prevalence of HDH amongst patients with ESRD undergoing MHD at our hospital, assess its clinical characteristics, its impact on the patients' mood, associated factors and the measures used by patients for its management.

Materials and Method

We conducted a questionnaire-based cross-sectional study amongst patients with ESRD undergoing MHD at a tertiary

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care medical hospital and teaching facility in western part of India after getting prior approval from the Institutional Research Ethics Committee. All patients who consented and were undergoing MHD regularly for more than 6 months were included in the study. ICHD 3 beta classification for HDH was used to diagnose HDH in these patients [Table 1]. Patients with baseline intracranial pathology which could lead to headache like recent head trauma, stroke, infection, tumor, and those with comorbid delirium/dementia were excluded. Visual analogue scale (VAS),[4] a validated scale to assess pain severity was administered to estimate the subjective intensity of headache and patient health questionnaire-9 (PHQ-9) was administered for screening, diagnosing and measuring severity of depression in the patients undergoing maintenance HD.[5] Pre-dialysis and post-dialysis blood pressure were recorded using a manual sphygmomanometer. Biochemical parameters consisting of serum sodium, potassium, creatinine, urea, magnesium were recorded along with the etiology of chronic renal failure. Patients were inquired about the measures taken to control the headache including the consumption of tea or coffee during hemodialysis sessions. The data was compiled and analyzed using independent *t* test and chi square test.

Results

A total of 131 patients fulfilling inclusion and exclusion criteria were approached, out of which 3 refused consent for participating in the study. Amongst 128 patients studied, 82 (64%) were men and 46 (36%) were women. Majority of the patients developed ESRD secondary to hypertension (28, 58%) followed by diabetes mellitus with hypertension (9, 19%) followed by mineral bone disorder (6, 13%). The mean age of the patients was 47.2 ± 17.3. 48 (37.5%) patients were diagnosed to have HDH. Amongst those having HDH, 18 (37.5%) were men and 30 (62.5%) of them were women. The site of headache was frontotemporal (22, 46%), frontal (18, 38%), temporal (3, 6%), parietal (3,6%), and occipital (2, 4%). The time of onset of HDH in 25 (52.08%) patients was between the first and second hours of HD session and the duration for which headache persisted after the hemodialysis session ended, in 34 (70.83%) participants, was within 1 h of completion of hemodialysis. Amongst the patients with HDH, 17 (13.28%) patients had begun experiencing HDH at the first dialysis itself. Amongst the patients with HDH, 20 (41.67%) (P = 0.003) had a baseline headache disorder before initiating dialysis, but 28 (58.33%) developed HDH de-novo. The mean (standard deviation [SD]) VAS scores for severity of pain were 4.5 ± 1.74 and median (IQR) was 4.5 (3–7). Patients having HD headache showed a mean score of 7.56 ± 4.51 on PHQ9, whereas patients not experiencing HD headache showed a mean score of 2.58 ± 1.63 [Table 2].

Table 1: International Classification of Headache Disorders 3: 10.2 Dialysis Headache

Headache with no specific characteristics occurring during and caused by hemodialysis. It resolves spontaneously within 72 h after the hemodialysis session has ended.
Diagnostic criteria:
At least three episodes of acute headache fulfilling criterion C
The patient is on hemodialysis
Evidence of causation shown by at least two of the following:
each headache has developed during a session of hemodialysis
either or both of the following:
a) each headache has worsened during the dialysis session
b) each headache has resolved within 72 h after the end of the dialysis session
headache episodes cease altogether after successful kidney transplantation and termination of hemodialysis
Not better accounted for by another ICHD-3 diagnosis.

*ICHD: International Classification of Headache Disorders

The difference in mean pre-dialysis diastolic blood pressure (DBP) values of patients with and without HDH was significant (P = 0.02). No significant difference was found in the electrolyte levels between patients having HDH and without HDH. Patients who were having thrice a week hemodialysis session had increased frequency of headache (27, 56.26%) (P = 0.01) as compared to patients on twice a week hemodialysis session (21, 44.75%) (P = 0.01). Patients with HDH had hypertension (28, 58%), bone mineral disorder (6, 13%), a combination of diabetes mellitus and hypertension (9,19%), combination of hypertension and mineral bone disorder (4, 6%), and other etiologies (1, 4%) as cause of CKD. There was no significant association between the etiology of ESRD and occurrence of HDH [Table 2]. Out of 48 patients with HDH, 17 (35%) developed headache during their first ever session of hemodialysis. 20 (41.2%) patients with HDH had a baseline primary headache disorder prior to diagnosis of ESRD. 28 (58.3%) patients with HDH had a de-novo headache disorder after initiation of HD for ESRD. 13 (16.25%) patients had a baseline primary headache disorder, but still did not develop HDH [Table 2].

The dialyzers used were bicarbonate based and the surface area of the dialyzer membrane was 1.3 mm^2, 1.5 mm^2 or 1.7 mm^2. On assessing the re-utilization of a dialyzer, it was seen that 34 (70.83%) patients having HDH were on single use dialyzers whereas 14 (29.17%) patients having HDH were on reusable dialyzers (P = 0.53). There was no significant association between presence of HDH and the surface area or characteristic of dialyzer. All participants in our study were provided with complimentary tea or coffee during the hemodialysis sessions by the hospital and so a relationship between HDH and caffeine consumption could not be studied. 41 (85%) patients in our study having HDH needed paracetamol in a dose of 500-650 mg to control their headache during the HD session, whereas 7 (15%) just took rest for remission of headache.

Discussion

This study which was initiated to find the prevalence of HDH found that nearly one-third (37.5%) of patients with ESRD undergoing dialysis experience HDH in a tertiary care hospital

Table 2: Characteristics of hemodialysis Headache

Characteristic	HDH Present (48)	HDH Absent (80)	*P*
Sex Male *n* (%)	18 (22)	64 (78)	<0.001
Female *n* (%)	30 (65)	16 (35)	
Age Mean (SD)	47.2 (17.3)	51.4 (14.9)	0.150
Etiology of ESRD	***n* (%)**	***n* (%)**	**Total**
Mineral Bone Disorder + Hypertension	4 (80)	1 (20)	5
Diabetic Nephropathy	0	2 (100)	2
Hypertensive Nephrosclerosis	28 (33)	58 (67)	86
Mineral Bone Disorder	6 (67)	3 (33)	9
Diabetes Mellitus + Hypertension	9 (38)	15 (62)	24
Others	1 (50)	1 (50)	2
Possible Relations with HDH	**Mean (SD)**	**Mean (SD)**	***P***
Pre HD SBP	166.16 (28)	163.88 (26)	0.642
Post HD SBP	156.35 (27)	155.91 (26)	0.927
Pre HD DBP	95.16 (22)	87.66 (15)	0.021
Post HD DBP	85.87 (14)	83.86 (17)	0.486
Serum Creatinine	7.81 (2.57)	7.94 (2.68)	0.787
Serum Potassium	5.11 (0.76)	5.6 (4.02)	0.409
Serum Urea	92.5 (30.4)	92.13 (36.33)	0.954
Serum Sodium	135.33 (3.85)	135.2 (6.54)	0.900
Serum Albumin	3.11 (0.49)	3.04 (0.54)	0.464
Hemoglobin	10.44 (1.57)	10.14 (1.9)	0.360
Dialysis Characteristics			
Frequency Of HD	***n* (%)**	***n* (%)**	**Total**
Twice a week	21 (44)	54 (66)	75
Thrice a week	27 (56)	26 (33)	53
Duration of Hemodialysis	***n* (%)**	***n* (%)**	**Total**
3 h	1 (2)	0	1
4 h	47 (98)	80 (100)	127
Dialyzer Usage	***n* (%)**	***n* (%)**	**Total**
First Use	34 (71)	61 (76)	95
Re-use	14 (29)	19 (23)	33
Possible Association			***P***
PHQ9 Mean (SD)	7.56 (4.51)	2.58 (1.63)	<0.001
Depression Yes *n* (%)	39 (81)	11 (14)	<0.001
Presence of Headache Disorder at Baseline	***n* (%)**	***n* (%)**	**Total**
Yes	20 (42)	13 (16)	43
No	28 (58)	67 (84)	95
Headache associated with First HD session	***n* (%)**	***n* (%)**	**Total**
Yes	17 (35)	0	17
HDH Characteristics	**Category**	**Frequency (%)**	
Site of Headache	Frontotemporal	22 (46)	
	Frontal	18 (38)	
	Temporal	3 (6)	
	Parietal	3 (6)	
	Occipital	2 (4)	
Time elapsed between start of HD and onset of Headache	***n* (%)**		
<60 min	12 (25)		
60-120 min	13 (27)		
120-180 min	10 (21)		
>180 min	13 (27)		

Contd...

Table 2: Contd...

Duration of HDH	*n* (%)
<60 min	34 (71)
60-120 min	12 (25)
120-180 min	1 (2)
>180 min	1 (2)
Treatment	***n* (%)**
Paracetamol	41 (85)
Rest	7 (14)

Table 3: Comparison of current study with other published studies on HDH

Author	Year	Country	Sample Size	HDH Prevalence	Site	Duration [h]	Depression	Remarks
Antoniazi *et al* [7]	1998-1999	USA	132	28 (21%)	NA	NA	NA	Only frequency assessed
Göksan *et al*.[6]	1996-2000	Turkey	63	30 (48%)	Frontotemporal (50%)	<4: 63% 4-24: 37%.	NA	Females had more HDH. Differences in Pre and post HD blood urea were associated with HDH
Goksel *et al*.[8]	2005	Turkey	250	70 (30%)	Vertex (41%)	5.17±5 h	NA	Pre HD serum sodium was higher in HDH patients.
Biljana *et al*.[21]	2014	Serbia	409	286 (70%)	bilateral	<4 h	NA	Both HD and peritoneal dialysis were assessed
Jesus *et al*.[12]	2009	Brazil	163	11 (6.7%)	Diffuse temporal	≤ 4 h in 72.7%;	NA	Low prevalence in this study
Farrokhi *et al*.[14]	2013	Canada	21055	NA	NA	NA	HR-1.51 (95% CI, 1.35-1.69)	Measured association of depression amongst HD patients and Mortality
Cukor *et al*.[15]	2013	USA	65	NA	NA	NA	48.5%	Assessed treatment effect on QOL in patients
Current Study	2020	India	128	48 (38%)	Frontotemporal (46%), bilateral	<1 h in 71%	39 had depression	Assessed depression too. HDH patients had more depression. Pre-HD BP and depression associated with HDH

NA: not assessed/not available in the study; HDH: Hemodialysis related Headache; VAS: Visual analogue scale; USA: United States of America; HR: Hazards Ratio

in India. Various studies have reported similar results [Table 3].[6-8] Amongst the patients with HDH, nearly one-tenth of them started to have headaches from the first dialysis session itself. Few studies have reported that patients who developed headache during their first hemodialysis session were more susceptible to develop headache during the subsequent sessions and fulfil the ICHD 3 criteria of HDH. Patients with a previous diagnosis of a primary headache disorder showed higher risk of developing HDH.[9] In our study, nearly forty percent of the patients with HDH had a pre-existing headache disorder. It may be debatable whether a pre-existing headache disorder should be considered as a risk factor for development of HDH or whether it should be considered as a confounding variable. The ICHD classifies HDH separately as a different headache disorder based on well-defined criteria irrespective of presence or absence of pre-existing headache in the past and so we consider pre-existing headache as a risk factor for development of HDH. The common site of occurrence of headache was

bilateral fronto-temporal region (22,46%) in majority of the participants. This study also revealed that headache was observed more among women (62.5%) than men (32.5%). This finding is similar to the study by Göksan *et al.*[6] but contrasting to findings of the study conducted by Alan. We also found that the mean (SD) severity of pain on VAS was 4.54 ± 1.74 and median (Interquartile Range) was 4.5 (3,7). This was similar to other studies which also showed moderate intensity headache in a majority of patients. In our study, nearly three-fourth of patients with HDH developed headache after the first hour of the hemodialysis session. In another study, 56.6% experienced HDH in the final hour of the session. A similar finding (62%) was also observed by Antoniazzi *et al.*, whereas Jesus *et al.* found that 27.3% patients experienced HDH in the final hour.[10-12] We also found that most patients having HDH were suffering from mild to moderate depression compared to patients without HDH. Depression has been described to be a common comorbidity in patients with headache disorders. We had found a prevalence of depressive disorders in nearly half of patients with primary headache disorders in our outpatient neurology clinics.[13] It may be possible that patients who are depressed are more susceptible to develop HDH which in turn worsens depression and affects quality of life. It could also be possible that having headache frequently during the dialysis may be worsening the quality of life, leading to depression. The patients who have poor scores on PHQ9 are expected to have a negative impact on their quality of life too. Similar results were obtained in other studies by Farrokhi *et al.*[14] and Cukor *et al.*[15] Thus, presence of HDH may lead to depression along with poor quality of life, making it important to find strategies to reduce HDH in order to improve the QOL of patients with ESRD undergoing HD.

We analyzed factors that might be associated with the occurrence of HDH. We found a significant difference ($P = 0.02$) between the pre-dialysis DBP amongst the patients with HDH and without HDH. This was similar to the results of Goksan *et al.*[6] except that they found significant differences in pre-dialysis SBP levels as well. Bana *et al* observed that hypertensive patients with headache and concluded that headache develops only when the blood pressure decreases rapidly from very high to low levels, and does not occur in patients with raised BP.[1] This decline in BP may trigger a mechanism similar to that of some anti-hypertensive drugs which cause headache due to dilation of cerebral blood vessels.[6] We also analyzed if the etiology of ESRD had any association with HDH and did not find and significant relationship between these. We did not find any significant difference in the pre dialysis serum values of creatinine, urea or electrolytes amongst patients with HDH and without HDH. Our finding is similar to the findings of Goksel *et al*.[8] We also found that more than half of patients experiencing HDH were undergoing thrice a week hemodialysis session ($P = 0.01$). It is possible that the patients undergoing more frequent HD had more biochemical alterations and fluctuations in blood pressure with associated cerebral blood flow changes leading to headache. The possible etiological factors that might trigger the headache are the abrupt biochemical changes during the hemodialysis session, dialysis disequilibrium syndrome, fluctuations in serotonin level, changes in renin aldosterone levels, hypoxia in the brain during the session.[11] We analyzed if the dialysis technique, dialyzer membrane and dialyzer characteristics had any association with occurrence of HDH. We found that 1.3 mm^2 membranes were more commonly used and the majority of patients (95, 74.2%) were on single-use dialyzers only. Amongst these, 34 (35%) patients experienced HDH. The technical aspects of dialysis did not have significant association with occurrence of HDH. Thus, the mechanisms of occurrence of HDH are myriad, multifactorial and difficult to assess or define due to multiple associated co-morbidities as confounders amongst the patients with ESRD on MHD. A recent study from Morocco suggested that renal replacement therapy like online hemodiafiltration gave superior results in terms of reduced incidence of HDH.[16] Further studies assessing how dialysis strategies can change frequency and severity of HDH would be required. We also evaluated the different modalities of treatment used by patients for treatment of HDH. For acute pain, paracetamol was the most frequently used and was administered by the dialysis nurse during the dialysis session on an as and when required basis. A randomized controlled trial conducted by Morais *et al.*[17] using non pharmacological methods like watching comedy movies during sessions showed significant improvement in depression, anxiety, and QOL in patients undergoing HD. In that trial, the patients in the experimental group also experienced less episodes of headache and hypertension during sessions.[17] However, the trail was not specifically addressing HDH based on ICHD 3 classification. A few medications such as angiotensin-converting enzyme inhibitors, amitriptyline, magnesium substitution, chlorpromazine, botulinum toxin have been suggested as prophylactic treatment for HDH however no randomized controlled trials (RCT) evaluating medicines for prophylaxis of HDH have been conducted.[18] There are a few studies assessing the role of caffeine in prevention and treatment of HDH with the presumption that caffeine withdrawal may be one of the reasons for development of HDH.[2] But a study that assessed HDH in patients by randomizing and allowing patients to the experimental group who received coffee with the control group who received a placebo found no evidence of decreased incidence or prevention of headaches.[19] As the patients with HDH have ESRD, non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase II (COX –II) inhibitors are contra-indicated in these patients. Hence focusing on RCTs to evaluate for adequate prophylactic therapy of HDH should be the next step in its management to improve quality of life of patients.

There were a few limitations in our study. We had collected details of headache in the first session of HD retrospectively in all patients and there is a possibility of recall bias in this information. Low blood values of Magnesium have been reported as a potential risk factor for HDH[6] but we could not measure post dialysis magnesium levels in all patients and so

association between serum magnesium and HDH could not be evaluated. We could not assess the values of CGRP and substance P before and after dialysis to assess their role in the genesis of HDH because of unavailability of these tests in our region.[20] We wanted to evaluate if caffeine had any role in HDH but we found that all patients undergoing HD in the hospital were being served complimentary tea or coffee by the hospital during the dialysis session and so the relevance of caffeine with HDH could not be assessed in our study. Another limitation to studies on HDH is its non-specific nature, making it hard to study and correlate the different clinical characteristics with the comorbidities. This is the reason for the paucity of research on this not uncommon disorder. Our study, which is an attempt to study this common yet neglected disorder in our region, depicts a high prevalence of HDH in our patients and points to need of further research on the pathophysiology and treatment of this disorder.

Conclusions

Nearly one-third of patients with ESRD on MHD have HDH. It is more common in women, is associated with moderate pain and depression. The factors contributing to HDH are still not well-characterized. With increasing cases of ESRD, and with such a high prevalence of HDH amongst such patients, identifying and alleviating risk factors for HDH is of utmost importance along with a planned approach to manage HDH. Further studies with a targeted approach to assess efficacy of different postulated treatment modalities is the need of the hour.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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